2015-016 Frataxin Knock-Down Mouse Model for Friedreich's Ataxia

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Technology description

BACKGROUND

Friedreich’ s Ataxia (FRDA) is a debilitating, life-shortening, degenerative neuromuscular disorder that is caused by severely reduced levels of frataxin. It affects about one in 50,000 people in the United States, but currently there are no treatments. Therefore the generation of corresponding mouse models is vital for understanding and designing better therapeutic strategies. However, because the organismwide frataxin knockdown is embryonically lethal, existing FRDA animal models either exhibit mild symptoms, or only have reduced frataxin in selected tissues.

INNOVATION

UCLA researchers have developed an inducible mouse model for Friedreich’ s Ataxia (FRDA), which allows reversal of frataxin knockdown. This allows researchers to circumvent the lethal effect of organism-wide knockout, while permitting significant frataxin reduction in all tissues. The researchers created a mouse line for FRDA by genomic integration of a single copy shRNA transgene (doxycycline-inducible) under the control of H1 promoter against Fxn gene that can mediate frataxin silencing temporally by inserting in a defined locus of the genome. Fxn knockdown can be controlled by the dose of doxycycline.

By producing an inducible and reversible frataxin knockdown mechanism in mice, Dr. Geschwind’ s group has created a means to control the onset and progression of disease in a mammalian animal model. By enabling control and reversal of the disease progression, the mouse model can achieve up to 90% temporal knockdown of frataxin.

It is also the first FRDA animal model that exhibits various symptoms parallel to human patients, including cardiac atrophy, elevated iron-responsive proteins, neurodegeneration, motor neuropathy–and for the first time in an FRDA model–scoliosis and ataxia. Thus, these mice are valuable as research tools for exploring the pathogenesis of FRDA and robust models to test and develop diagnostics and therapeutics for FRDA.

Advantages

Organism-wide frataxin knockdown (up to 90%)

Inducible: able to control the onset and progression of the disease
Reversible: able to reverse the acceleration of disease progression
Exhibit various symptoms parallel to FRDA patients

Institution

University of California, Los Angeles

Inventors

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